1007-174 Clopidogrel Regulates Platelet, Leukocyte, and Endothelial Interactions in Type 2 Diabetes Mellitus

Jaydeep Sarma, Scott A. Harding, Jehangir Din, Paul Macioca, David E. Newby, Keith A. A. Fox, University of Edinburgh, Edinburgh, United Kingdom

Introduction
Patients with diabetes mellitus have an increased risk of developing atherosclerosis and its sequelae. Atherosclerosis is now recognized to be an inflammatory disease involving multiple interactions between platelets, leukocytes and endothelial cells. We examined whether specific platelet ADP receptor inhibition with the thienopyridine clopidogrel reduced platelet-monocyte binding, monocyte activation and endothelial activation, in patients with type 2 diabetes mellitus.
Methods
Twenty patients with type 2 diabetes mellitus received clopidogrel 75mg daily for 28 days. Platelet surface P-selectin and CD40L ligand (CD40L) expression, monocyte surface CD40 and CD11b expression, platelet-monocyte binding (PMB) and platelet-neutrophil binding (PNB) were assessed by flow cytometry; plasma soluble (s)CD40L and soluble (s)E-selectin were assessed by ELISA; the chemokines RANTES and MCP-1 were assessed by flow cytometric bead array, before and after treatment.
Results
Significant reductions were seen in platelet surface P-Selectin (p=0.002), PMB (p=0.007) and PNB (p=0.0025), and also monocyte surface CD40 (p=0.007) and CD11b (p=0.0245) after clopidogrel treatment. No significant changes occurred in platelet surface CD40L (p=0.61), nor in plasma levels of sCD40L (p=0.24), sE-selectin (p=0.44) and MCP-1 (p=0.8175), but there was a highly significant reduction in plasma RANTES, (p<0.0001).
Conclusions
Clopidogrel acts to reduce platelet and leukocyte activation and adhesion in type II Diabetes Mellitus, suggesting a potential anti-inflammatory effect of thienopyridines. The lack of change in sE-selectin and the specific reduction in the platelet-derived chemokine RANTES suggests that these effects are platelet-driven, and not due to altered endothelial function.

1007-175 Antithrombotic Effects of Angiotensin II Receptor Blockade

David A. Vorchheimer, Mohammad Urooj Zafar, Anuragini Pandey, Ida C. Guzman, Jose Rodriguez, Bharathi Reddy, Mitchell A. Cohen, Juan J. Badimon, Mount Sinai Medical Center, New York, NY, AstraZeneca LLP, Wilmington, DE

Background: Angiotensin II accelerates the development and progression of atherothrombosis. Treatment with angiotensin receptor blockers (ARB) can reverse endothelial dysfunction, reduce oxidant stress, and inhibit inflammation. Recent large clinical trials demonstrate that ARB therapy can slow or prevent the progression of coronary artery disease. The clinical benefits observed in these trials suggested benefit beyond blood pressure reduction, perhaps via alternate mechanisms. **Methods:** We used the Badimon perfusion chamber to study the effects of a selective angiotensin II type 1 receptor antagonist (candesartan) on platelet-vessel wall interaction in 23 patients with cardiovascular disease. Thrombus formation was assessed at low (212/s) and high (1690/s) shear rates, which mimic the rheologic conditions seen in venous blood and mildly stenotic coronary arteries. Thrombus formation was measured before and after 6 weeks treatment with candesartan (16mg/day) in addition to other standard treatments for CAD. **Results:** Baseline demographic features of the population included age 61±11years, 48% males, with the following CAD risk factors: 78% had hypertension, 52% had diabetes, and 91% had hyperlipidemia. Candesartan reduced systolic (133±20 to 115±12 mm Hg) and diastolic (80±10 to 75±8 mm Hg) blood pressure. Thrombus formation was reduced from 2644±231 to 1960±224 μ/mm^2 (Δ =26.5%, p<0.001) at low shear rate, and from 7756±552 to 5502±394 μ/mm^2 (Δ= 27.5%, p<0.001) at high shear rate. However, there was no correlation between inhibition of thrombus formation and systolic (r=0.218) or diastolic (r=0.076) blood pressure reduction. **Conclusion:** Short-term ARB treatment significantly reduced platelet-thrombus formation in patients with cardiovascular disease. This antithrombotic effect appeared to be independent of blood pressure reduction. Ongoing clinical trials will determine whether this antithrombotic effect will translate into clinical benefits of ARB therapy for post MI patients.

1007-176 Peroxisome Proliferator Activated Receptor Gamma Agonist Protects Against Arterial Thrombosis in a Mouse Model of Insulin Resistance

Peter F. Bodary, Fernando B. Vargas, Susan Davis King, Michael T. Purkey, Kevin J. Wickenheiser, Daniel T. Eitzman, University of Michigan, Ann Arbor, MI

Background The prevalence of insulin resistance and diabetes is increasing in the U.S. Both insulin resistance and diabetes are associated with a marked increase in cardiovascular disease mortality although the mechanisms responsible for this increased risk are largely unknown. Since thrombosis occurring at sites of vascular disease accounts for the vast majority of cardiovascular complications in insulin resistant patients, we hypothesized that directly improving insulin sensitivity with a peroxisome proliferator activitated receptor gamma (PPARγ) agonist may be effective in reducing the thrombotic response following vascular injury. **Methods and Results**. A model of obesity and insulin resistance was used that involved feeding mice of the KK strain a high fat diet for 2 weeks (n=12). Mice were then provided standard rodent chow and divided into two groups to receive either pioglitazone (a synthetic PPARγ ligand, 0.012% food admixture) (n=5) or placebo (n=7). Mice receiving the pioglitazone had significantly reduced fasting plasma glucose, leptin, insulin and triglyceride levels with increased adiponectin concentrations after 2.5 weeks of treatment. To determine if pioglitazone treatment was associated with a beneficial effect on thrombosis following vascular injury, mice were subjected to photochemical injury of the carotid artery. Mice receiving placebo formed an occlusive thrombus 11.3 ± 1.0 minutes following the initiation of injury while mice receiving pioglitazone formed an occlusive thrombus in 22.3 ± 3.9 minutes (p<0.05). No effect of pioglitazone was observed in euglycemic C57BL/6 mice (n=4 per group) suggesting that the beneficial effect of pioglitazone requires pre-existing insulin resistance. **Conclusion**. The PPARγ agonist pioglitazone provides protection against thrombosis in a mouse model of obesity and insulin resistance.

1007-177 Predictors of Major Hemorrhage Following Initiation of Warfarin Therapy

Henock Saint-Jacques, Anne S. Hellkamp, David E. Kandzari, Christopher M. O' Connor, Robert Daly, Stephen L. Kopecky, Anatoly Langer, David Vorchheimer, Patrick T. O' Gara, Valentin Fuster, Robert M. Califf, Robert A. Harrington, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

Background: Despite documented benefits of oral anticoagulant therapy for patients (pts) at risk for embolic events, use of warfarin remains low mostly secondary to concerns for major hemorrhage (MH). **Objective:** We identified pts characteristics that predict MH after initiation of a uniform dosing of warfarin. **Methods:** Among pts in the Coumadin Aspirin Reinfarction Study (CARS) who were randomized to a daily fixed dose of warfarin 3mg combined with aspirin 80 mg, INR levels were measured at the end of the first week of therapy by a core laboratory using the same thromboplastin reagent (ISI=0.97). MH was defined as intracranial hemorrhage or spontaneous bleeding that required surgical intervention, a decrease in hemoglobin ≥ 2 g/dL or sufficient to require transfusion, or bleeding that contributed to death, impaired sight or hearing. Multivariable Cox proportional hazard model was developed to assess the relationship between baseline pts characteristics and MH. **Results:** MH occured among 64 out of 2,913 pts over median (25^{th},75^{th} percentile) = 151(51, 340) days after initiation of therapy. MH was associated with increasing age, non-white ethnicity, higher INR levels or BMI, and use of adrenergic agents. Concomitant use of beta blockers had a protective effect. **Conclusion:** These data identify important pts characteristics that are predictive of warfarin-associated MH. Clinicians are encouraged to account for these modifiable risk factors and identify high-risk groups when initiating warfarin therapy.

Predictors of major hemorrhage among 2913 patients following initiation of warfarin therapy.

Variables	P-value	HR (95% CI)
Age	0.0001	1.32 (1.17, 1.50) for 5 years increase
INR	0.0001	1.15 (1.07, 1.23) for 0.5 unit increase
Beta blockers use	0.002	0.45 (0.27, 0.74)
Non-white race	0.006	2.29 (1.26, 4.16)
BMI	0.051	1.05 (1.00, 1.09) for each unit increase
Adrenergic agents use	0.061	2.31 (0.96, 5.52)

1007-178 Elevated Levels of Hemostatic Markers in Patients With Atrial Fibrillation and Aortic Atherosclerosis

Keiko Nakagawa, Tadakazu Hirai, Tomoki Kameyama, Noriko Shinokawa, Hidetsugu Asanoi, Hiroshi Inoue, Toyama Medical and Pharmaceutical University, Toyama, Japan

Background: Patients (pts) with atrial fibrillation (AF) are at risk for thromboembolism, and their prothrombotic profiles might be associated with coexistent cardiovascular disease, rather than AF alone.
Methods: In 63 pts with AF and 42 pts with normal sinus rhythm (NSR) who underwent transesophageal echocardiography, plasma levels of markers for platelet activity (β-thromboglobulin and platelet factor 4), thrombotic status (thrombin-antithrombin III complex (TAT) and prothrombin fragment F1+2 (F1+2)) and fibrinolytic status (plasmin-α2-plasmin inhibitor complex and D-dimer) were determined. Thromboembolic risk and severity of aortic atherosclerosis were evaluated by transesophageal echocardiography.
Results: Pts with AF, as a whole, had higher hemostatic markers and severe left atrial spontaneous contrast than those in NSR. F1+2 and fibrinolytic markers in pts with severe atherosclerosis (atheroma ≥ 5mm and/or mobile plaque) were significantly elevated as compared with that of pts without severe atheroma. Particularly, AF pts with severe atherosclerosis showed significantly higher levels of F1+2 and fibrinolytic markers than in those without atherosclerosis, while markers for platelet activity were not significantly different between AF pts with and without severe atherosclerosis (Figure). **Conclusion:** Pts with severe aortic atherosclerosis coexistent with AF appear to have an increased risk for thromboembolism, and could benefit from more intensive antithrombotic therapy.